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Effects of Chlordimeform on Cardiovascular Functional Parameters. Part 2. Acute and Delayed Effects Following Intravenous Administration in the Postweanling Rat

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16. ABSTRACT

The differential effects of intravenous (IV) and intraperitoneal (IP) administration of chlordimeform (CDM) were investigated in 22 - 30 day old pentobarbital-anesthetized Sprague-Dawley rats. The first group of animals (N = 25) were given sequential IV injections of 5, 10, 30, 60, and 120 mg/kg CDM, or normal saline vehicle followed by a single injection of 60 mg/kg CDM. Heart rate (HR), arterial blood pressure (BP), and electrocardiogram (ECG) were monitored for all animals. CDM produced profound acute effects on all cardiovascular parameters monitored and persistent delayed effects on HR and BP. These effects were similar to but less severe than those observed in a previous study using geriatric animals. The second group of animals (N = 32) received a single IP injection of either 10, 30, or 60 mg/kg CDM, or normal saline vehicle. The decrease in HR produced by CDM in these animals was comparable to the delayed HR effect seen in the first group despite the differences in dosing regimens and routes of administration.

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a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

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EFFECTS OF CHLORDIMEFORM ON CARDIOVASCULAR FUNCTIONAL PARAMETERS: PART 2. ACUTE AND DELAYED EFFECTS FOLLOWING INTRAVENOUS ADMINISTRATION IN THE POSTWEANLING RAT

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The effects of intravenous (iv) administration of chlordimeform (CDM) were investigated in 22- to 30-d-old pentobarbital-anesthetized Sprague-Dawley rats. Animals (n = 25) were given sequential iv injections of 5, 10, 30, 60, and 120 mg CDM/kg, or normal saline vehicle followed by a single injection of 60 mg CDM/kg. Heart rate (HR), arterial blood pressure (BP), and electrocardiogram (ECG) were monitored for all animals, while body temperature was maintained at control levels (37°C). CDM produced profound acute effects on all cardiovascular parameters monitored and persistent delayed effects on HR and BP. These effects were similar to but less severe than those observed in a previous study using geriatric animals. Younger animals also appeared to be more resistant to the lethal actions of CDM.

INTRODUCTION

Chlordimeform [*N'*-(4-chloro-*o*-tolyl)-*N,N*-dimethylformamidine, Galecron, Fundal, CDM], a prototypical pesticide of the formamidine group used in the control of ticks and mites, has been shown to produce potent depressive effects on mammalian cardiovascular function (Hayes, 1982; Lund et al., 1978a). Intravenous exposure to sublethal doses of CDM in the anesthetized, geriatric rat elicits both acute and delayed responses (Watkinson, 1985). The acute effects are dose-related and transitory in nature and include abrupt decreases in heart rate and systemic blood pressure as well as arrhythmic responses and alterations in electrocardiographic waveform parameters. The delayed

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response is less pervasive but more persistent and is primarily characterized by sustained decreases in heart rate and blood pressure. Lethal doses are rapidly effective, producing cardiac and/or respiratory collapse.

Despite extensive investigation, the mechanism whereby CDM exerts these toxic effects is still unclear (Chinn et al., 1977; Lund et al., 1978b; Robinson and Smith, 1977). It is unlikely that any of the major actions attributable to CDM (e.g., inhibition of monoamine oxidase, relaxation of vascular smooth muscle, increased stabilization of cellular membrane, etc.) can entirely account for the observed cardiovascular effects (Benezet et al., 1978; Lund et al., 1979). The present study was conducted as part of a continuing investigation to document the actions of CDM on mammalian cardiovascular function and to further elucidate the mechanisms involved. In particular, this study examined the effects obtained in response to intravenous administration of CDM in postweanling rats. Data were compared with results obtained from the previous study (Watkinson, 1985) to investigate potential age-related differences in the toxic response.

METHODS

Animals

Young Sprague-Dawley rats were used in this study. Animals were obtained (Charles River Breeding Laboratory, Kingston, N.Y.) at 21 d of age, the earliest possible time following weaning. Until studied, they were housed in plastic cages on pine-shaving bedding in a temperature-controlled (22–26°C) and light-controlled (12 h light, 12 h dark) biologically clean room. They were allowed access to tap water and laboratory feed ad libitum. Animals were of both sexes and ranged in age from 22 to 30 d old. The weight range for the female rats was 64–94 g, while the male rats ranged from 59 to 103 g.

Experimental Preparation

The experimental preparation for this study was similar to that described previously for the study using geriatric animals (Watkinson, 1985). Briefly, animals were anesthetized with sodium pentobarbital and placed on a heated water table (surface T = 32°C). Catheters (either PE-10 or PE-50 tubing, depending on the size of the animal) were implanted in the right jugular vein for infusion of test solutions and in the right carotid artery for monitoring pulsatile arterial blood pressure (BP). Subcutaneous electrodes were placed at the juncture of the extremities to monitor the electrocardiogram (ECG). Heart rate (HR) was obtained from the ECG, and mean arterial blood pressure (MABP) was electronically derived from the pulsatile pressure signal. All data were monitored on an eight-channel chart recorder and recorded on mag-

netic tape using a four-channel FM cassette recorder. ECG parameters were analyzed as previously described (Watkinson et al., 1985).

Experimental Procedure

The experimental procedure followed for the present study was similar to that of the previous study using geriatric animals. A total of 25 animals were used for this study. Animals were paired by sex and weight and randomly assigned to treatment or control groups. ECG, HR, BP, and MABP were monitored continuously throughout the experimental procedure. In most cases, lead II of the ECG was routinely monitored, with brief recordings of leads I and III obtained for comparative purposes before and after experimental treatments. A stabilization period of 15–30 min was allowed for recovery from the surgical procedures before control recordings were obtained. Rats in the treatment group were injected with sequential iv doses of 5, 10, 30, 60, and 120 mg CDM/kg (chlordimeform HCl, 98% pure; Chem Service, Westchester, Pa.) dissolved in normal saline. All concentrations were adjusted so that the volumes administered were equivalent to 1 μl/g body weight. In addition to the preinjection ECG data, ECG parameters were quantitated before and after each injection. Injections were spaced 10–15 min apart to permit recovery from the acute effects and to allow the cardiovascular parameters monitored to return toward steady-state levels. All test solutions were administered slowly over a period of 45–60 s and were followed by infusion of a small volume of heparinized saline (100 IU/ml). Animals in the control group were given similarly adjusted volumes of vehicle only. These injections followed a time course comparable to that of the CDM-treated animals and were also followed by small volumes of heparinized saline. After the final saline injection, animals in the vehicle-treated group were given a single iv injection of 60 mg CDM/kg and subsequently monitored for at least 20 min.

Statistical Analysis

Statistical analysis was conducted using the general linear models procedure of the Statistical Analysis System (SAS Institute, 1982). The least square means procedure was used to test for differences between groups. Probability values less than 0.05 were considered significant.

RESULTS

Characteristic Response

The characteristic response pattern of the cardiovascular parameters following iv injection of CDM in young rats was essentially the same as that described in the previous study involving geriatric rats (Watkinson, 1985). This overall response can be divided into two

chronological phases. Briefly, the acute portion of the response consisted of an abrupt dose-related decrease in both HR and BP, followed by a reflexive overshoot of these parameters above preinjection levels. Significant arrhythmias often occurred in conjunction with these effects. The HR and BP rapidly peaked and gradually returned toward original steady-state levels, while the ECG waveform quickly resumed its preinjection configuration. The delayed portion of the response occurred approximately 10–15 min postinjection. At this time, there was a significant decrease in HR and BP over a time span of 1–2 min. These new lower levels were maintained throughout the duration of the experiment. Non-rate-related changes in ECG waveform parameters were minimal during the delayed portion of the response.

Heart Rate Response

For analytical purposes, the HR data have been divided into acute-response or delayed-response classifications, although it is emphasized that these groupings are experimentally derived and represent discrete samples of a continuous variable. The acute values were obtained during the period immediately following injection and represent the period of greatest depression of the cardiovascular parameters. This nadir generally occurred immediately after the saline flush. The delayed values were derived from samples obtained approximately 15 min postinjection and represent both the postinjection steady-state value and the control value for the subsequent injection. Thus, there are four values associated with each CDM injection: (1) the initial preinjection control value, (2) the immediate preinjection control value, (3) the acute value, and (4) the delayed value. These groupings permit analyses of the overall acute effect and the delayed effect, as well as the magnitude and percent change from both the initial preinjection control value and the immediate preinjection control value. The HR data for the vehilce-treated control group were similarly classified. These data are shown in Table 1 and Fig. 1*a*.

There was no significant difference between the initial preinjection HR of the vehicle- and CDM-treated groups (Table 1). The HRs of the vehicle-treated control group rose slightly over the course of the experimental procedure. There was a significant and precipitous drop in HR in the treatment group (acute HR values) following CDM exposure when compared to either the initial preinjection control value, the immediate preinjection value, or the time-paired vehicle-treated control group value. In addition, the recovery or steady-state HRs (delayed HR values) were all significantly lower than the initial preinjection control values and the time-paired vehicle-treated animal HRs.

All HR values were normalized with respect to their preinjection control values, and these data are shown in Fig. 1*a*. There are several noteworthy points concerning this graph. First, the delayed decrease in

HR following the initial 5 mg/kg injection of CDM, with respect to the preinjection control, was greater than the decrease associated with the acute response. Second, the magnitude of the acute decrease in HR was greater for each successive dose in the CDM-treated group. Third, there was a larger dose-response effect on the acute portion of the HR response than on the delayed portion of this response, as indicated by the steeper negative slope of the dotted lines connecting these respective data points. Finally, it is possible to compare the effect on HR of a single nonlethal iv injection of 60 mg CDM/kg in a group of animals not previously exposed to CDM (vehicle-treated controls) with that in a group of animals subjected to cumulative increasing doses of CDM (CDM-treated group). While the actual magnitude of the acute decrease in HR in beats per minute (bpm) following the single iv 60-mg/kg injection in the vehicle-treated control group was much larger than that following the same dosage in the cumulatively injected CDM-treated group (168 versus 99 bpm), the percentage decrease from the respective preinjection steady-state value for the two treatments is comparable (38.6% versus 30.0%). Furthermore, although the actual acute HR value was lower for the cumulative-treated group (267 versus 232 bpm), in large part due to its lower preinjection control value, the delayed or recovery values for the two groups following iv injection of 60 mg CDM/kg were nearly identical (311 versus 315 bpm).

Blood Pressure Response

The BP response was essentially similar to the HR response. These data have been classified and analyzed in the same manner as reported above and are shown in Table 1 and Fig. 1*b*. As in the previous study, the MABP of the vehicle-treated group rose over the course of the experiment while the MABP of the CDM-treated animals dropped precipitously. The magnitude of the decrease in MABP during the acute portion of the response in the CDM-treated animals was dose-related and significantly different from the initial preinjection control, the immediate preinjection control, and the time-paired vehicle-treated control for each injection. The sustained MABP level—e.g., the delayed response value—was also significantly decreased when compared to the initial preinjection control value and the MABP of the time-paired vehicle-treated control group. The delayed effects on MABP were not dose-related.

Electrocardiographic Response

Waveform Parameters. The changes in ECG waveform parameters, although similar, were not as striking in the present study as in the study involving aged animals. The mean values of these parameters obtained during the acute response to each injection for both vehicle- and CDM-treated groups are shown in Table 1. These data confirm the

TABLE 1. Heart Rate, Mean Arterial Blood Pressure, and Electrocardiographic Waveform Parameter Values for Intravenous Vehicle- and Chlordimeform-Treated Postweanling Rats

Parameter	Preinjection	Vehicle treatment, 1	Vehicle treatment, 2
HR (bpm)	418.00 ± 14.00[b]	423.00 ± 14.00	430.00 ± 13.00
MABP (mm Hg)	79.00 ± 5.00	80.00 ± 5.00	81.00 ± 4.00
P–T Interval[a] (ms)	143.24 ± 5.92	145.18 ± 5.86	143.35 ± 5.92
P–R Interval (ms)	40.53 ± 1.08	40.93 ± 1.07	39.89 ± 1.32
R–αT Interval (ms)	27.23 ± 1.23	27.75 ± 1.31	27.07 ± 1.20
R–T Interval (ms)	102.71 ± 5.66	104.26 ± 5.77	103.46 ± 5.27
S–T Interval (ms)	91.93 ± 5.61	93.54 ± 5.74	92.99 ± 5.40
P-Wave duration (ms)	13.60 ± 0.55	13.73 ± 0.64	13.28 ± 0.93
QRS Duration (ms)	13.92 ± 0.54	14.24 ± 0.65	13.90 ± 0.79
T-Wave duration (ms)	88.79 ± 5.53	90.02 ± 5.67	89.56 ± 5.07
P–R Segment (ms)	26.92 ± 0.91	27.20 ± 0.78	26.61 ± 0.82
S–T Segment (ms)	3.14 ± 0.39	3.52 ± 0.51	3.43 ± 0.61
S–αT Segment (ms)	16.44 ± 1.04	17.03 ± 1.12	16.60 ± 1.15
αT–P Segment (ms)	75.49 ± 5.86	76.51 ± 6.13	76.40 ± 5.87

Parameter	Preinjection	Chlordimeform treatment, 5	Chlordimeform treatment, 10
HR (bpm)	451.00 ± 11.00	394.00 ± 15.00[d]	344.00 ± 10.00[d]
MABP (mm Hg)	93.00 ± 3.00	85.00 ± 3.00[c]	63.00 ± 4.00[d]
P–T Interval (ms)	135.01 ± 3.56	161.26 ± 9.99	191.06 ± 8.02[d]
P–R Interval (ms)	39.08 ± 0.97	37.51 ± 1.52	40.15 ± 1.27
R–αT Interval (ms)	26.35 ± 0.84	25.84 ± 1.15	24.08 ± 0.58
R–T Interval (ms)	95.93 ± 3.17	123.75 ± 9.27	150.91 ± 7.50[d]
S–T Interval (ms)	85.18 ± 3.12	113.21 ± 9.25	139.96 ± 7.66[d]
P-Wave duration (ms)	12.55 ± 0.50	12.79 ± 0.92	13.83 ± 0.83
QRS Duration (ms)	13.96 ± 0.43	13.88 ± 0.27	14.43 ± 0.53
T-Wave duration (ms)	81.97 ± 3.20	109.86 ± 9.23	136.48 ± 7.74[d]
P–R Segment (ms)	26.53 ± 0.83	24.72 ± 1.41	26.32 ± 1.49
S–T Segment (ms)	3.22 ± 0.29	3.35 ± 0.27	3.48 ± 0.36
S–αT Segment (ms)	15.60 ± 0.91	15.31 ± 1.10	13.13 ± 0.53
αT–P Segment (ms)	69.58 ± 3.20	97.91 ± 8.87	126.83 ± 7.55[d]

[a] Definitions of electrocardiographic intervals, waves, and segments have been modified for the rat ECG. Although the terminology used is similar to traditional clinical usage, slight differences exist. For definition of terms, see Watkinson et al. (1985).

injection number				
3	4	5	60 mg/kg	At 15 min post 60 mg/kg
435.00 ± 14.00	434.00 ± 15.00	436.00 ± 20.00	267.00 ± 17.00[d]	311.00 ± 17.00[d]
79.00 ± 4.00	80.00 ± 3.00	78.00 ± 3.00	44.00 ± 6.00[d]	51.00 ± 5.00[d]
137.92 ± 5.13	136.56 ± 4.51	137.54 ± 5.66	218.86 ± 13.70[d]	193.61 ± 10.29[d]
38.99 ± 0.85	38.71 ± 1.12	37.11 ± 0.99	42.02 ± 2.25[c]	40.90 ± 1.18
25.50 ± 1.28	26.26 ± 1.55	27.56 ± 1.26	27.31 ± 0.82	30.73 ± 2.01
98.92 ± 4.73	97.85 ± 3.79	100.43 ± 4.89	176.84 ± 14.11[d]	152.71 ± 9.44[d]
88.15 ± 4.81	87.16 ± 3.90	89.87 ± 5.03	163.97 ± 13.71[d]	141.13 ± 9.24[d]
13.51 ± 0.62	13.39 ± 0.69	12.57 ± 0.86	19.23 ± 1.52[d]	12.88 ± 0.98
13.76 ± 0.46	13.92 ± 0.62	13.65 ± 0.67	17.24 ± 0.87[c]	14.93 ± 0.44
85.17 ± 4.60	82.93 ± 3.66	86.78 ± 5.03	159.60 ± 13.46[d]	137.78 ± 9.22[d]
25.48 ± 0.72	25.32 ± 0.96	24.54 ± 0.84	22.78 ± 0.86	28.03 ± 0.83
2.98 ± 0.32	3.24 ± 0.47	3.09 ± 0.59	4.37 ± 0.38[c]	3.35 ± 0.37
14.73 ± 1.29	15.57 ± 1.59	17.00 ± 1.26	14.43 ± 0.88	19.15 ± 1.88
73.42 ± 5.25	71.59 ± 4.49	72.87 ± 5.92	149.54 ± 14.20[d]	121.99 ± 9.03[d]

dose (mg/kg)		
30	60	120
278.00 ± 11.00[d]	232.00 ± 16.00[d]	187.00 ± 28.00[d]
48.00 ± 2.00[d]	33.00 ± 3.00[d]	24.00 ± 4.00[d]
206.11 ± 9.47[d]	254.45 ± 13.39[d]	267.10 ± 13.30[d]
44.92 ± 1.44[d]	55.08 ± 2.42[d]	62.42 ± 2.66[d]
24.18 ± 0.51	32.20 ± 3.24[d]	32.15 ± 2.35[d]
161.19 ± 8.63[d]	199.37 ± 14.20[d]	204.67 ± 12.76[d]
149.82 ± 8.56[d]	182.49 ± 14.23[d]	188.54 ± 12.61[d]
15.03 ± 0.81[c]	17.64 ± 1.38[d]	18.02 ± 1.14[d]
15.63 ± 0.46	23.17 ± 1.51[d]	24.18 ± 1.86[d]
145.56 ± 8.44[d]	176.20 ± 14.11[d]	180.49 ± 12.35[d]
29.89 ± 1.43[c]	37.44 ± 1.97[d]	44.40 ± 2.92[d]
4.26 ± 0.39[c]	6.29 ± 0.41[d]	8.05 ± 0.75[d]
12.80 ± 0.53	15.32 ± 1.86	16.02 ± 1.32
137.02 ± 8.50[d]	167.18 ± 14.27[d]	172.52 ± 11.79[d]

[b] Each value represents mean ± SEM for 6–15 animals.
[c] Indicates significance at $p \leq 0.05$.
[d] Indicates significance at $p \leq 0.001$.

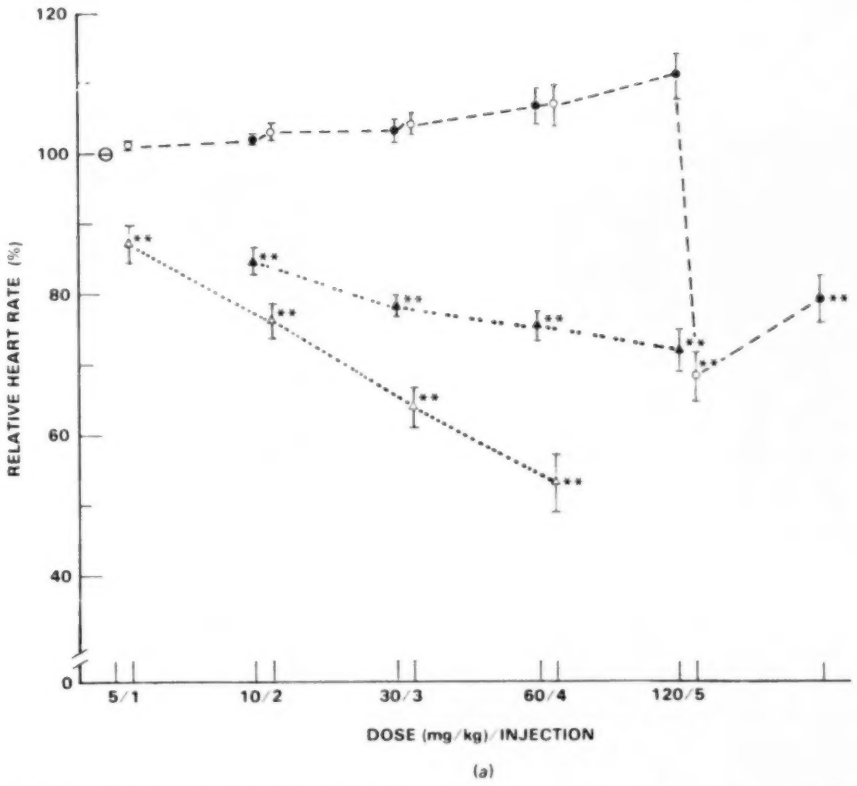
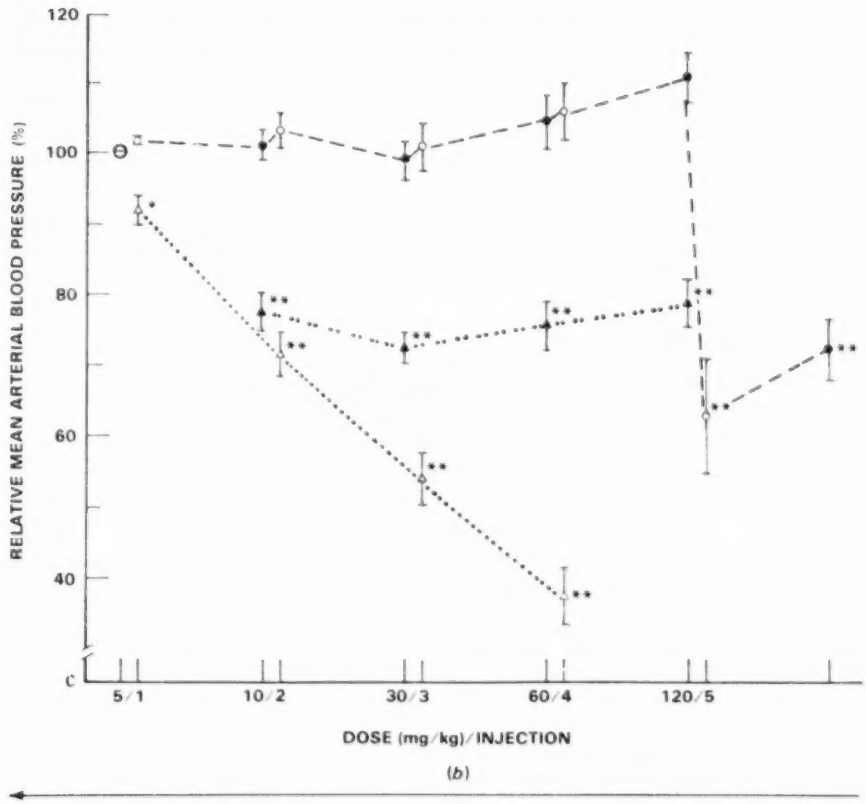


FIGURE 1. Relative (a) HR and (b) MABP responses (means ± SEM; n = 6–15) of postweanling rats to sequential intravenous injections of CDM or normal saline vehicle. Data were first normalized with respect to preinjection values. Circle with bar (⊖) indicates initial control value for both groups. Circles indicate data from vehicle-treated control group, and triangles indicate data from CDM-treated group. Solid symbols indicate preinjection control values, and open symbols indicate postinjection values. Dashed line shows chronological sequence of values for vehicle-treated group animals. Single and double dotted lines demarcate consecutive acute and delayed response values, respectively. Values shown on the abscissa indicate either dose (for the CDM-treated animals) or injection number (for the vehicle-treated animals). Note that the final injection in the vehicle-treated group was with 60 mg CDM/kg. Data obtained following exposure to CDM were compared to either the appropriate time-paired values from the vehicle-treated control group (for the values in the CDM-treated group) or the immediate preinjection control value (for the final two values in the vehicle-treated control group). Significantly different values are indicated as follows: $^{*}p \leq 0.05$, $^{**}p \leq 0.001$.



(b)

previously observed trend toward dose-related lengthening of the components within the ECG following exposure to CDM.

Arrhythmias. The frequency and severity of arrhythmias induced following iv exposure to CDM were also markedly attenuated in the young animals when compared to the aged animals. The most commonly observed arrhythmias included sporadic premature atrial and premature ventricular contractions, which progressed to bigemy and atrioventricular block at the higher dose ranges. Although the types of arrhythmias observed were similar, the responses as a rule required larger doses to initiate and were of shorter duration. It was rare for arrhythmias to occur during the time period following cessation of the acute response and prior to the subsequent injection.

Lethality

In general, young animals tolerated lower doses of CDM better and survived higher doses when compared to older animals. Of the animals

exposed to the cumulative dosing regimen, 1, 2, and 2 animals died following administration of 10, 30, and 60 mg CDM/kg, respectively. None of the animals survived exposure to 120 mg CDM/kg iv. However, 77.2% of the young rats from the vehicle-treated group given a single iv injection of 60 mg CDM/kg survived, in contrast to the similarly treated aged rats, which all died. As in the previous study, lethality appeared to be due to rapid induction of an acute response of sufficient magnitude that it prevented recovery. Components of this response included rapid, severe, and irreversible bradycardia, hypotension, and arrhythmias, followed by cardiac and respiratory arrest.

DISCUSSION

In general, the present study employing iv administration of CDM to postweanling rats confirmed and extended the observations of the previous study using geriatric animals (Watkinson, 1985). In both studies, there were similar acute and delayed effects on HR and BP. The acute effects were dose-related and transient, while the time-delayed depressive effects were persistent and did not exhibit a significant dose-response relationship. Both ECG rhythm and waveform parameters were affected acutely, while the differences observed during the delayed portion of the response were primarily confined to rate-related effects only. Higher doses of CDM administered iv were rapidly lethal, producing asystole within a few seconds. Death appeared to result from a combination of cardiac and respiratory arrest.

The differences between the results of these studies utilizing animals of varying ages were primarily quantitative in nature. Generally, the magnitudes of the responses, both acute and delayed, were greater in the older rats and less severe in the younger animals. The percent decreases in HR and BP were lower in the young animals. The variety and severity of rhythm disturbances and waveform perturbations were also markedly attenuated when compared to the aged animals and required higher thresholds to initiate. Finally, the younger animals appeared more resistant to the lethal action of CDM, an effect noted previously by Robinson and Smith (1977). It was not uncommon for the postweanling animals to recover from the acute toxic response following iv injection of 60 mg CDM/kg, whereas none of the aged rats (n = 16) survived the 60-mg/kg dose.

The biphasic nature of the toxic effect on HR and BP is clearly illustrated in Figs. 1 *a* and *b*. It is readily apparent that the lines connecting the acute and delayed response values represent distinct processes, both of which differ significantly from the control response. This is shown by the differences in the slopes of the response lines as well as the differences in the magnitudes of the decreases between successive acute and delayed response values. The dichotomy of the action of

CDM is further illustrated by the time course of the observed effects. The time between the onset of the acute response and the onset of the delayed response and the transient and persistent character of the respective effects provide strong evidence for the dual-effect hypothesis. A final indicator of mechanistic differences in the toxic response concerns the effect consistently observed following the initial exposure to CDM at 5 mg/kg. Thus, during a period of relatively stable cardiovascular parameters following the cessation of the acute response, there was an abrupt, additional decrease in HR and MABP that exceeded that of the initial effect.

While the results of the present study clearly establish the existence of a biphasic response across age groups, many questions remain concerning the mechanisms responsible for these separate effects. As discussed previously (Watkinson, 1985), there is evidence to indicate that the acute effects observed following CDM administration may be the result of a direct action of CDM on the musculature and conduction system of the heart, followed by a centrally mediated cardiac reflex response. These dose-related effects are rapidly induced and dissipated. The mechanism(s) responsible for the delayed actions of CDM is less well defined. It is not known whether the entire response is mediated by CDM or if it is partially effected by the action of a metabolite. Also, it is not clear whether these actions are directed on the heart, the peripheral vasculature, or the central nervous system. It is tempting to speculate that the lack of a significant dose-response effect may indicate that the delayed response is attributable to mechanisms different from those producing the acute response and that these mechanisms are saturated at relatively lower dose levels of CDM exposure. Further, in view of the available evidence, it seems likely that the delayed response is at least partially attributable to the action of a metabolite of CDM on the vascular smooth muscle of the peripheral resistance vessels as well as on the pacemaker or conduction tissue of the heart.

Additional discussion concerning the delayed response observed in the present study following iv exposure to CDM is presented in conjunction with the results from a companion study that follows (Watkinson, 1986).

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